



Atty. Docket No. 081356/0156  
Appl. Serial No. 09/720,970

**IN THE UNITED STATES PATENT AND TRADEMARK OFFICE**

In re patent application of

Hideaki NOMURA *et al.*

Serial No.: 09/720,970

Group Art Unit: 1616

Filed: January 3, 2001

Examiner: Sharmila S. Gollamudi

For: POWDERY PREPARATION FOR MUCOSAL  
ADMINISTRATION CONTAINING POLYMERIC MEDICINE

**DECLARATION UNDER 37 CFR § 1.132**

Commissioner for Patents  
Washington, D.C. 20231

Sir:

I, Hideaki Nomura, declare that

1. I am a citizen of Japan.
2. I am employed as a product planner at Pharmaceutical Division of Kirin Beer Kabushiki Kaisha, at 26-1, Jingumae 6-chome, Shibuya-ku, Tokyo, 150-8011 Japan. I was transferred from Iyaku Kaihatsu Kenkyusho (Pharmaceutical Research Laboratory), Kirin Beer Kabushiki Kaisha, 3 Miyahara-cho, Takasaki-shi, Gunma 370-1295, Japan on November 1, 2001. I graduated from Science University of Tokyo, where I obtained a master's degree in Pharmaceutical Science in 1988 and pharmacist license in 1986. I entered Kirin Beer Kabushiki Kaisha and I have been engaged in the study of pharmaceutical formulation of new chemical and protein therapeutic agents.
3. I am a co-inventor of the U.S. application serial number 09/720,970, entitled "*Powdery Preparation For Mucosal Administration Containing Polymeric Medicine*," filed on January 3, 2001.
4. The present invention relates to a preparation comprising an aminoalkylmethacrylate copolymer that increases the rate of absorption of a high molecular weight medicine through an individual's mucosa, such as their nasal mucosa.

Atty. Docket No. 081356/0156  
Appl. Serial No. 09/720,970

5. I have reviewed the Office Action mailed on October 25, 2002, and the prior art cited therein, and understand that the Examiner has rejected the claims as obvious over the prior art.

6. The Examiner takes the position that "the applicant has not provided any unexpected results using the instant polymers," and that, therefore, "the claims are rejected as *prima facie* obvious," page 4 of the October 25, 2002, Office Action.

7. The person of ordinary skill in the art, however, would not have expected the substitution of chitosan or DEAE-dextran with a copolymethacrylate of WO 90/09870.

8. Drugs can be absorbed through the mucosa via the paracellular or the intercellular space of a "tight junction" of mucosal tissue.

9. It is via the intercellular space that Applicants consider to be important for the absorption of high molecular weight and hydrophilic medicines through mucosa.

10. It was our unexpected finding that an aminoalkylmethacrylate copolymer, such as Eudragit E100, is superior than DEAE-dextran, chitosan, or poly-L-arginine in transporting substances through the intercellular space.

11. I conducted the experiments related in Examples [insert\*] of the present application, as well as those related in Experiments 1 and 2, which are appended to this Declaration.

12. "Experiment 1" shows, as do the Experimental Examples in the application, that the aminoalkylmethacrylate copolymer, Eudragit E100 is approximately 10-times superior in its ability to transport substances through the intercellular space than DEAE-dextran, chitosan, or poly-L-arginine.

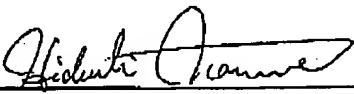
13. "Experiment 2" illustrates that the aminoalkylmethacrylate copolymer is approximately 100-times better at enhancing the transmission of G-CSF through the mucosal intercellular space, than DEAE-dextran, chitosan, or poly-L-arginine.

\*\*\*\*\*

Atty. Docket No. 081356/0156  
Appl. Serial No. 09/720,970

I hereby declare that all the statements made herein of my known knowledge are true and that all statements made on information and belief are believed to be true; and further, that these statements are made with the knowledge that willful false statements are so made punishable by fine or imprisonment, or both, under Section 101 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issuing thereon.

June 20, 2003  
Date

  
Hideaki Nomura

## Reference 1

The effect of various transmission-enhancing agent on in vitro transmission through membrane of substances using Caco-2 as a model membrane is examined.

Experiment 1. The effect of various transmission-enhancing agent on transmission of mannitol, which is a marker passing through intercellular space

concentration of agent (%)	transmission coefficient (cm/s)			
	Eudragit E-100	DEAE-Dextran	Chitosan	Poly-L-Arginine
0.000	2.1E-07	2.1E-07	2.1E-07	2.1E-07
0.001	2.4E-07	-	-	-
0.005	5.8E-06	-	-	-
0.010	2.3E-05	-	-	-
0.050	3.6E-05	-	-	-
0.100	3.2E-05	2.6E-07	3.4E-07	9.4E-07
0.500	3.8E-05	2.3E-07	8.3E-07	1.9E-06
1.000	3.5E-05	2.5E-07	5.1E-07	2.5E-06
5.000	3.0E-05	1.6E-06	2.9E-06	5.7E-06

note: 2.1E-07 means  $2.1 \times 10^{-7}$ .

Experiment 2. The effect of various transmission-enhancing agent on transmission of G-CSF

concentration of agent (%)	transmission coefficient (cm/s)			
	Eudragit E-100	DEAE-Dextran	Chitosan	Poly-L-Arginine
0.000	<5.0E-08	<5.0E-08	<5.0E-08	<5.0E-08
0.010	5.2E-07	<5.0E-08	<5.0E-08	<5.0E-08
0.050	2.4E-06	<5.0E-08	<5.0E-08	<5.0E-08
0.100	2.9E-06	<5.0E-08	<5.0E-08	<5.0E-08
0.500	4.1E-06	<5.0E-08	<5.0E-08	<5.0E-08
1.000	3.8E-06	<5.0E-08	<5.0E-08	<5.0E-08

note: <5.0E-08 means "below  $5.0 \times 10^{-8}$ ", which is lower limit of determination.

# EUDRAGIT®

The complete range of  
acrylic polymers

## SUSTAINED CONTROLLED RELEASE



Enteric Coatings

Sustained  
Controlled Release

Protective Coatings  
& Taste Masking

Coating  
Calculator

To calculate your own coating

**EUDRAGIT® RL 30 D** highly permeable  
pH independent polymer for sustained  
release aqueous formulations



**EUDRAGIT® RL PO** highly permeable pH  
independent polymer for matrix formulations

**EUDRAGIT® RL 100** highly permeable pH  
independent polymer insoluble in water

**EUDRAGIT® RS 30 D** pH independent polymer  
with low permeability for sustained release  
aqueous formulations

**EUDRAGIT® RS PO** pH independent polymer with  
low permeability for matrix formulations

**EUDRAGIT® RS 100** pH independent polymer  
insoluble in water with low permeability

**EUDRAGIT® NE 30 D** neutral ester copolymer for  
wet granulation in sustained release formulations

**EUDRAGIT® NE 40 D** neutral ester copolymer  
with 10% more solids for wet granulation in  
sustained release formulations

## EUDRAGIT®

The complete range of  
acrylic polymers

Enteric Coatings

Sustained  
Controlled Release

Protective Coatings  
& Taste Masking

Coating  
Calculator

To calculate your own coating

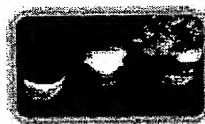
## PROTECTIVE COATINGS & TASTE MASKING



**EUDRAGIT® E 100** pH dependent cationic polymer soluble in gastric fluid up to pH 5.0 - swellable and permeable above pH 5.0 for taste and odor masking applications

**EUDRAGIT® EPO** powder form of EUDRAGIT E-100 for aqueous formulations

**EUDRAGIT® RD 100** pH independent fast disintegrating film for aqueous taste & odor masking formulations



VIDEO

30 second disintegration of  
EUDRAGIT® RD 100 in water